AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

Claims 1-13 (Canceled).

14. (Currently Amended) ~~The method of claim 13~~ A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary in the plurality of response profiles, wherein the cellular constituents which co-vary are identified by cluster analysis of cellular constituents in the plurality of response profiles, wherein the cluster analysis is done by means of ~~wherein~~ the clustering algorithm ~~is~~ *hclust*, wherein said plurality of response profiles comprises at least five response profiles, and wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations.

Claims 15-17 (Canceled).

18. (Currently Amended) ~~The method of claim 17~~ A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular

constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary in the plurality of response profiles, wherein the cellular constituents which co-vary are identified by cluster analysis of cellular constituents in the plurality of response profiles, wherein said plurality of response profiles comprises at least five response profiles, wherein said cluster analysis is carried out by a hierarchical clustering method, wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations, wherein a statistical significance for the sets of co-varying cellular constituents is determined by means of an objective statistical test, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents an actual fractional improvement in the cluster analysis of the cellular constituents based on the unpermuted responses of said cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of cellular constituents by means of Monte Carlo randomization of perturbation index for the response of each cellular constituent across all perturbations;

(c) performing said cluster analysis on the permuted responses of cellular constituents;

(d) determining for each cluster which is generated in step (c) and defines a set of co-varying cellular constituents the fractional improvement in the cluster analysis of cellular constituents based on the permuted responses of cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the cellular constituents is obtained for

each said cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents;

wherein the statistical significance of each of said sets of co-varying cellular constituents is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

Claims 19-21 (Canceled).

22. (Currently Amended) ~~The method of claim 21~~ A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, and wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations,

wherein the one or more sets of cellular constituents are identified by re-ordering the response profiles into sets associated with similar biological effects, wherein the sets of response profiles associated with similar biological effects are identified by cluster analysis of the response profiles done by means of ~~wherein~~ the clustering algorithm ~~is~~ *hclust*.

Claims 23-25 (Canceled).

26. (Currently Amended) ~~The method of claim 25~~ A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or

downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, and wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations,

wherein the one or more sets of cellular constituents are identified by re-ordering the response profiles into sets associated with similar biological effects, wherein the sets of response profiles associated with similar biological effects are identified by cluster analysis of the response profiles, wherein said cluster analysis is carried out by a hierarchical clustering method, wherein a statistical significance for the sets of response profiles is determined by means of an objective statistical test, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of response profiles an actual fractional improvement in the cluster analysis of the unpermuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituent index for each response profile across the measured cellular constituents;

(c) performing said cluster analysis on the permuted response profiles;

(d) determining for each cluster which is generated in step (c) and defines a set of response profiles the fractional improvement in the cluster analysis of the permuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the response profiles is obtained for each said cluster which is generated by said cluster analysis and defines a set of response profiles;

wherein the statistical significance of each of said sets of response profiles is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

Claims 27-46 (Canceled).

47. (Currently Amended) ~~The method of claim 46~~ A method for grouping measured response profiles in sets which are associated with similar biological effects comprising grouping response profiles among a plurality of response profiles into sets, each of said sets of response profiles consisting of response profiles in which the responses of one or more sets of genes in each response profile are similar among response profiles in the set, each response profile in said plurality of response profiles (i) comprising measurements of transcript levels of a plurality of genes, and (ii) resulting from a different perturbation, wherein each of said sets of genes consists of genes that co-vary under a plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, wherein the sets of response profiles are identified by cluster analysis of the response profiles done by means of ~~wherein~~ the clustering algorithm ~~is~~ *hclust*.

Claims 48-49 (Canceled).

50. (Currently Amended) ~~The method of claim 49~~ A method for grouping measured response profiles in sets which are associated with similar biological effects comprising grouping response profiles among a plurality of response profiles into sets, each of said sets of response profiles consisting of response profiles in which the responses of one or more sets of genes in each response profile are similar among response profiles in the set, each response profile in said plurality of response profiles (i) comprising measurements of transcript levels of a plurality of genes, and (ii) resulting from a different perturbation, wherein each of said sets of genes consists of genes that co-vary under a plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at

least five response profiles, wherein the sets of response profiles are identified by cluster analysis of the response profiles, wherein said cluster analysis is carried out by a hierarchical clustering method, wherein a statistical significance for the sets of response profiles is determined by means of an objective statistical test, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of response profiles an actual fractional improvement in the cluster analysis of the unpermuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted response profiles by means of Monte Carlo randomization of gene index for each response profile across the measured genes;

(c) performing said cluster analysis on the permuted response profiles;

(d) determining for each cluster which is generated in step (c) and defines a set of response profiles the fractional improvement in the cluster analysis of the permuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the response profiles is obtained for each cluster which is generated by said cluster analysis and defines a set of response profiles;

wherein the statistical significance of each of said sets of response profiles is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

Claims 51-60 (Canceled).

61. (Currently Amended) ~~The method of claim 60~~[[,]] A method for determining the therapeutic efficacy of a drug or drug candidate comprising identifying one or more groups of

sets of cellular constituents in one or more response profiles associated with exposure to the drug or drug candidate, each response profile comprising measurements of a plurality of cellular constituents, wherein each of said groups is indicative of a particular therapeutic effect, and wherein the therapeutic effect of the drug or drug candidate is determined to be the particular therapeutic effect indicated by the identified groups, wherein each of said sets of cellular constituents consists of cellular constituents that co-vary under a plurality of perturbations or that are co-regulated, wherein the sets of cellular constituents are determined by a method comprising performing cluster analysis of the response profiles done by means of ~~wherein~~ the clustering algorithm ~~is~~ *hclust*.

Claims 62-63 (Canceled).

64. (Currently Amended) ~~The method of claim 63~~ A method for determining the therapeutic efficacy of a drug or drug candidate comprising identifying one or more groups of sets of cellular constituents in one or more response profiles associated with exposure to the drug or drug candidate, each response profile comprising measurements of a plurality of cellular constituents, wherein each of said groups is indicative of a particular therapeutic effect, and wherein the therapeutic effect of the drug or drug candidate is determined to be the particular therapeutic effect indicated by the identified groups, wherein each of said sets of cellular constituents consists of cellular constituents that co-vary under a plurality of perturbations or that are co-regulated, wherein the sets of cellular constituents are determined by a method comprising performing cluster analysis of the response profiles, wherein said cluster analysis is carried out by a hierarchical clustering method, wherein a statistical significance for the sets of cellular constituents is determined by means of an objective statistical test, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of cellular constituents an actual fractional improvement in the cluster analysis of cellular constituents based on the unpermuted responses of said cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of cellular constituents by means of Monte Carlo randomization of the perturbation index for each cellular constituent across all perturbations;

(c) performing said cluster analysis on the permuted responses of cellular constituents;

(d) determining for each cluster which is generated in step (c) and defines a set of cellular constituents the fractional improvement in the cluster analysis of cellular constituents based on the permuted responses of cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the cellular constituents is obtained for each cluster which is generated by said cluster analysis and defines a set of cellular constituents;

wherein the statistical significance of each of said sets of cellular constituents is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

Claims 65-91 (Canceled).

92. (Currently Amended) ~~The method of claim 91~~ A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, and wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of

cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations,

wherein said sets of cellular constituents are co-varying cellular constituent sets that are identified by cluster analysis done by means of ~~wherein~~ the clustering algorithm ~~is~~ *hclust*.

Claims 93-95 (Canceled).

96. (Currently Amended) ~~The method of claim 95~~ A method of determining a consensus profile for a first plurality of drug perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of cellular constituents in a plurality of response profiles, whether said set of cellular constituents is upregulated or downregulated by each of said first plurality of drug perturbations, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different drug perturbation among said first plurality of drug perturbations to said type of cell or organism, wherein each set of cellular constituents in said plurality of sets of cellular constituents consists of cellular constituents that co-vary under a second plurality of perturbations or that are co-regulated, wherein said plurality of response profiles comprises at least five response profiles, and wherein said consensus profile for said first plurality of drug perturbations consists of measurements of said set or sets of cellular constituents that are determined in said determining step to be upregulated or downregulated by each of said first plurality of drug perturbations,

wherein said sets of cellular constituents are co-varying cellular constituent sets that are identified by cluster analysis, wherein said cluster analysis is carried out by a hierarchical clustering method, wherein a statistical significance for the sets of co-varying cellular constituents is determined by means of an objective statistical test, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents an actual fractional improvement in the cluster analysis of the cellular constituents based on the unpermuted responses of said cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of

said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of cellular constituents by means of Monte Carlo randomization of the perturbation index for response of each cellular constituent across the set of perturbations;

(c) performing said cluster analysis on the permuted responses of cellular constituents;

(d) determining for each cluster which is generated in step (c) and defines a set of co-varying cellular constituents the fractional improvement in the cluster analysis of cellular constituents based on the permuted response responses of cellular constituents, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the cellular constituents is obtained for each cluster which is generated by said cluster analysis and defines a set of co-varying cellular constituents,

wherein the statistical significance of each of said sets of co-varying cellular constituents is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

Claims 97-105 (Canceled).

106. (Currently Amended) ~~The method of claim 105~~ A method for grouping measured response profiles in sets which are associated with similar biological effects comprising grouping response profiles in sets among a plurality of response profiles by cluster analysis of said plurality of response profiles, said sets of response profiles consisting of response profiles having similar responses of a group of cellular constituents, each response profile in said plurality of response profiles (i) comprising measurements of a plurality of cellular constituents, and (ii) resulting from a different perturbation, wherein a statistical significance for the sets of response profiles is determined by means of an objective statistical test,

wherein said cluster analysis is carried out by a hierarchical clustering method, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of response profiles an actual fractional improvement in the cluster analysis of the unpermuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted response profiles by means of Monte Carlo randomization of cellular constituent index for each response profile across the measured cellular constituents;

(c) performing said cluster analysis on the permuted response profiles;

(d) determining for each cluster which is generated in step (c) and defines a set of response profiles the fractional improvement in the cluster analysis of the permuted response profiles, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the response profiles is obtained for each cluster which is generated by said cluster analysis and defines a set of response profiles;

wherein the statistical significance of each of said sets of response profiles is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

Claims 107-118 (Canceled).

119. (Currently Amended) ~~The method of claim 118~~ A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of genes in a plurality of response profiles, whether said set of genes is upregulated or downregulated by each of said first plurality of perturbations, each response profile in said plurality of response profiles (i)

comprising measurements of transcript levels for a plurality of genes, and (ii) resulting from a different perturbation among said first plurality of perturbations to said type of cell or organism, wherein each set of genes in said plurality of sets of genes consists of genes having transcripts that co-vary under a second plurality of perturbations or that are co-regulated, and wherein said consensus profile for said first plurality of perturbations consists of measurements of transcript levels for said set or sets of genes that are determined in said determining step to be upregulated or downregulated by each of said first plurality of perturbations,

wherein each of the sets of genes consists of genes which co-vary in the plurality of response profiles, wherein the genes which co-vary are identified by cluster analysis of genes in the plurality of response profiles, and wherein the cluster analysis is done by means of ~~wherein~~ the clustering algorithm ~~is~~ *hclust*.

Claims 120-122 (Canceled).

123. (Currently Amended) ~~The method of claim 122~~ A method of determining a consensus profile for a first plurality of perturbations to a cell type or organism, said method comprising determining, for each of a plurality of sets of genes in a plurality of response profiles, whether said set of genes is upregulated or downregulated by each of said first plurality of perturbations, each response profile in said plurality of response profiles (i) comprising measurements of transcript levels for a plurality of genes, and (ii) resulting from a different perturbation among said first plurality of perturbations to said type of cell or organism, wherein each set of genes in said plurality of sets of genes consists of genes having transcripts that co-vary under a second plurality of perturbations or that are co-regulated, and wherein said consensus profile for said first plurality of perturbations consists of measurements of transcript levels for said set or sets of genes that are determined in said determining step to be upregulated or downregulated by each of said first plurality of perturbations,

wherein each of the sets of genes consists of genes which co-vary in the plurality of response profiles, wherein the genes which co-vary are identified by cluster analysis of genes in the plurality of response profiles, wherein said cluster analysis is carried out by a hierarchical clustering method, wherein a statistical significance for the sets of co-varying

genes is determined by means of an objective statistical test, and wherein the objective statistical test comprises:

(a) determining for each cluster which is generated by said cluster analysis and defines a set of co-varying genes an actual fractional improvement in the cluster analysis of the genes based on the unpermuted responses of said genes, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster;

(b) generating permuted responses of genes by means of Monte Carlo randomization of perturbation index for the response of each gene across all perturbations;

(c) performing cluster analysis on the permuted responses of genes;

(d) determining for each cluster which is generated in step (c) and defines a set of co-varying genes the fractional improvement in the cluster analysis of genes based on the permuted responses of genes, wherein said fractional improvement is an improvement in total scatter with respect to the center of said cluster as compared to total scatter with respect to the respective centers of the two clusters branching out of said cluster; and

(e) repeating steps (b) through (d) so that a distribution of fractional improvements in the cluster analysis of the genes is obtained for each cluster which is generated by said cluster analysis and defines a set of co-varying genes;

wherein the statistical significance of each of said sets of co-varying genes is determined by comparing the actual fractional improvement for the cluster defining said set to the distribution of fractional improvements for the cluster defining said set.

124. (Canceled).